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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	US-126O	1750

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CERMAK & KENEALY LLP
ACS LLC
515 EAST BRADDOCK ROAD
SUITE B
ALEXANDRIA, VA 22314

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 77-84 are pending in the application.

[2] Applicant's amendment to the claims, filed on 4/2/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Claim 77 has been amended relative to the claim listing filed on 2/26/07.

[3] Receipt of an information disclosure statement, filed on 6/3/08, is acknowledged.

[4] Receipt of a terminal disclaimer, filed on 4/2/08, is acknowledged.

[5] Applicant's arguments filed on 4/2/08 in response to the Office action mailed on 2/1/08 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[7] The reference cited in the IDS filed on 6/3/08 has been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Claim Rejections - 35 USC § 103

[8] The rejection of claims 77-84 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi in view of Williams and as evidenced by Zakataeva and Hanko is withdrawn,

not in view of applicant's arguments, but instead upon further consideration and in favor of the rejection of claims 77-84 as being unpatentable over Kobayashi in view of Kaplan, Georgiou, and Begot and as evidenced by Zakataeva and Kruse as set forth below.

[9] The rejection of claims 77-84 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi in view of Williams and Kaplan and as evidenced by Zakataeva and Kruse is withdrawn, not in view of applicant's arguments, but instead upon further consideration and in favor of the rejection of claims 77-84 as being unpatentable over Kobayashi in view of Kaplan, Georgiou, and Begot and as evidenced by Zakataeva and Kruse as set forth below.

[10] The rejection of claim(s) 77-84 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi in view of Kaplan, Georgiou, and Begot and as evidenced by Zakataeva and Kruse is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 10 beginning at p. 10 of the 2/1/08 Office action.

RESPONSE TO ARGUMENT: Beginning at p. 5, bottom of the instant remarks, applicant argues:

> The claims are drawn to a method of producing an L-amino acid by 3 distinct manipulative steps. That is, step 1 is cultivating the bacterium, step 2 is removing solids including cells from the medium, and step 3 is purifying the L-amino acid from the medium obtained in step 2. These are distinct steps as indicated in the claim, for example, that the L-amino acid is purified from the medium obtained in the second step. Clearly, one cannot purify the L-amino acid recited in step 3 without first obtaining the medium in step 2, that is, a medium

having the solids, including cells, removed. Contrary to the teachings of any of the cited references, the desired product, the L-amino acid, is purified from the supernatent, that is the medium, after removing solids, including cells, from the medium. This is explicitly stated in the claims, in that step B states that the solids, such as the cells and cellular debris, are removed from the culture medium, and step C states that the L-amino acid is purified from the medium obtained in step B). It is undisputed that this medium is the supernatent obtained after removing the cells and cellular debris.

It is asserted that the Examiner has made an error in interpreting the claims, and as a result, has mis-applied the prior art. Specifically, Kobayashi is cited for teaching an *E. coli* host cell transformed with vector pAB t 04, which comprises a DNA segment which includes the region between and including genes pldA and pldB (see p. 1012, figure 4 and p. 1014, figure 6). This region includes the DNA of SEQ ID NO: 3, which encodes the amino acid sequence of SEQ ID NO: 4, as demonstrated by Zakataeva. Appellants have agreed with this interpretation of these references.

The newly cited Williams et al. is cited as the secondary reference to Kobayashi, in that it is to make up for the acknowledged deficiency of Kobayashi of NOT teaching steps B) and C) of claim 74, for example, purification of an L-amino acid including L-threonine. Williams et al. is cited for teaching the centrifugation of an *E. coli* culture for 10 minutes, and that one of ordinary skill in the art would recognize that during centrifugation, the cells become forced to the bottom of the tube and become the cell pellet, while the liquid portion of the culture medium remains above the pellet. The evidentiary reference of Hanko et al. is cited to show that LB medium contains L-amino acids, as was commonly known in the art.

Despite the newly cited secondary and evidentiary references, it remains the Applicants position that Kobayashi fails to teach the recovery or purification of an L-amino acid, nor even ally indication that an L-amino acid might be present in the medium following the cultivation and centrifugation of the cultivated cells, and the evidentiary references fail to make up for this deficiency. It is for these and the following reasons that the Examiner's interpretation of the claims is in error.

Specifically, the Examiner has cited to the teaching in Kobayashi, on page t 009 in the section entitled "Enzyme Assay" at the bottom of column 1, that the strain harboring the desired vector is cultured, and then the cells are 'spun down' and washed. The pellet, which contains the solids such as the cells and cellular debris, was further processed and the objective enzymes were further purified from the processed pellet. The medium is not used for any purpose and is likely discarded, as it is NOT further processed. There is no disclosure of recovering any substance from the medium or supernatent that remains after the 'spinning'. There is no disclosure that any substance *could be* isolated from the medium or supematent. More importantly, the reference of Kobayashi fails to teach, either explicitly or implicitly, step C of claim 1, that is, the purification of the L-amino acid from the medium obtained in step B.

The Examiner has stated that "by practicing the method of Kobayashi, one of ordinary skill in the art would be "removing solids" in accordance with step B and purifying said L-amino acid" in accordance with step C simultaneously." (see page 3 of the Office Action mailed April 16, 2007). The Examiner explains that the step of centrifuging the cells would simultaneously remove solids from the medium and purify the L-amino acid, which is in the cells, from the medium. This interpretation of the prior art and application to the claims is a clear error.

This is because the claims distinctly recite 3 manipulative steps, that is, cultivating the bacterium, removing solids including cells from the medium, and purifying the L-amino *acid from the medium* obtained in the second step. These are distinct steps as indicated in the claim, for example, that the L-amino acid is purified from the medium obtained in the second step. Clearly, one cannot purify the L-amino acid without first obtaining the medium in the second step, that is, a medium having the solids, including cells, removed. The Examiner has erred in interpreting steps B and C to be combined into one. It is clear that step C cannot be conducted without first obtaining the medium from step B. It is impossible to combine them for this reason. Merely separating the pellet with the cellular debris from the medium cannot be interpreted as "purifying the L-amino *acid from tile medium",* as the medium is only obtained as a result of this separation.

In the latest Office Action, the Examiner argues that the claim does not specify that *all* the cells would be removed from the medium, some may remain from which the L-amino acid would be purified, and that also, there are L-amino acids present in the LB medium as components of the medium which would likely be purified, thus satisfying the last two steps of the claimed method. However, the claims have been amended to recite that the L-amino acid to be purified is present in the remaining medium (after purification by centrifugation) is present in an amount larger than if the cells were cultured and not transformed. This is the crux of the invention not recognized by any of the cited prior art. Clearly, the references do not teach such an increase in amino acid production, nor would one of ordinary skill in the art expect such an increase based on the teachings of the references, either singly or combined.

Furthermore, Kobayashi teaches away from purifying L-amino acids from any cell culture since the only description of a culture method describes manipulation of the post-centrifugation pellet, which does not contain the objective L-amino acids. The term "purifying" as defined in the specification on page 23, lines 2-7 clearly indicates a manipulative step such as "ion exchange, concentration and crystalline fraction methods..." is performed, which is not described or suggested by the Enzyme Assay of Kobayashi. This represents a further clear error in the interpretation of the claim, as the Examiner has refused to read the claims' terms in light of the specification. Although it is acknowledged that the purification methods described in the specification at page 23 cannot be imported into the claim, Appellant's definition cannot be completely ignored. The Examiner is completely ignoring this definition in the specification, as it clearly indicates that the claim must be interpreted to actually indicate a purification of the amino

acid from the medium, not merely separating a medium from a pellet, as is taught by Kobayashi.

The application of Williams et al. to the claims does not overcome the shortcomings of Kobayashi, in that there is still no teaching of purifying an amino acid from the aliquot or the medium after removing the solids from the medium. Furthermore, one of ordinary skill must have a reason or motivation to combine the references *(KSR International Co. v. Teleflexlnc. et al.,* No. 04-1350, slip op. at t6 (S.Ct., April 30, 2007)), and there is no commonality in the teachings of these references that would provide a reason for the person of ordinary skill in the art to combine these teachings. Neither reference has the goal of producing an L-amino acid, nor discuss such production in reference to the methods taught. As neither reference teaches or suggests such a method or even the desire to obtain an L-amino acid, the methods taught by these references fail to render obvious the claimed method. There is no teaching in any of the 4 cited references of step C in the claimed method, nor any suggestion from the various teachings of centrifugation of the various cultures for the purpose of producing large amounts of a desired amino acid. Therefore, this reference adds nothing to the rejection and fails to render obvious the claimed invention.

At p. 9, bottom of the instant remarks, applicant also argues:

The teachings and lack thereof relative to the present invention of Kobayashi, Williams, Zakataeva are presented above. The reference of Kruse has been discussed in previous responses and in the Appeal Brief. The citation of Kaplan is new, and is discussed *infra.* Kaplan is cited for showing that *E. coli* is a well-known L-threonine producer. This fact is not disputed and is well-known in the art. Therefore, this reference adds no further weight to the rejection and the arguments presented above continue to apply. Specifically, there would be no motivation or reason to isolate a markedly increased amount of L-threonine from the medium after purifying the cells after centrifugation. In fact, as shown above, one of ordinary skill in the art would have assumed that the cells and all cellular products would be present in the pellet. Therefore, one of ordinary skill in the art would not have expected a large of amount of L-threonine in the medium at this point in the process of the claimed invention, and hence the invention is non-obvious over the cited prior art.

None of the references has the goal of producing an L-amino acid, nor discuss such production in reference to the methods taught. As none of the cited reference teaches or suggests such a method or even the desire to obtain an L-amino acid, the methods taught by these references fail to render obvious the claimed method. There is no teaching in any of the cited references of step C in the claimed method, nor any suggestion from the various teachings of centrifugation of the various cultures for the purpose of producing large amounts of a desired amino acid. Therefore, the Kaplan reference adds nothing to the rejection and fails to render obvious the claimed invention in combination with the other cited references.

At p. 10, bottom of the instant remarks, applicant further argues:

The teachings and lack thereof relative to the present invention of Kobayashi, Williams, Kaplan, and Zakataeva are presented above. The references of Kruse and Georgiou have also been discussed in previous responses and in the Appeal Brief. The citation of Begot is new, and is discussed *infra.* Begot, similar to Georgiou, is cited for showing that it was well-known to determine the growth phase of a bacterial culture medium by monitoring the optical density of the medium. This fact is not disputed, but fails to make up for the deficiencies of Kobayashi. Therefore, this reference adds no further weight to the rejection and the arguments presented above continue to apply. Specifically, there would be no motivation or reason to expect a markedly increased amount of L-threonine from the medium after purifying the cells after centrifugation. 'In fact, as shown above, one of ordinary skill in the art would have assumed that the cells and all cellular products would be present in the pellet. Of course, one might expect a very small amount of L-amino acid to be present in the medium, as it is known that LB medium contains amino acids. However, one of ordinary skill in the art would not have expected a large of amount of L-threonine in the medium at this point in the process of the claimed invention, and hence the invention is non-obvious over the cited prior art.

None of the references has the goal of producing an L-amino acid, nor discuss such production in reference to the methods taught. As none of the cited reference teaches or suggests such a method or even the desire to obtain an L-amino acid, the methods taught by these references fail to render obvious the claimed method. There is no teaching in any of the cited references of step C in the claimed method, nor rely suggestion from the various teachings of centrifugation of the various cultures for the purpose of producing large amounts of a desired amino acid. Therefore, the Begot reference adds nothing to the rejection and fails to render obvious the claimed invention in combination with the other cited references.

Applicant's argument is not found persuasive. It appears that applicant has taken an improperly narrow interpretation of the claims, requiring that "removing the solids…" step requires removing *all* solids, the "purifying said L-amino acid…" step can only be practiced after all cells are removed from the medium, and that steps B) and C) are discreet and cannot overlap or occur simultaneously. However, neither the claims nor the specification appears to require such an interpretation. Although applicant argues that "It is undisputed that this medium is the supernatent obtained after removing the cells and cellular debris", it is clear from the examiner's stated position in prior Office

actions that the "medium" of step C) is not required to be "the supernatent obtained after removing the cells and cellular debris".

The following comments are provided to aid in clarifying the rejection and appear to be undisputed by applicant. Regarding step B) of claim 77, the step of "removing solids including cells from the medium", it is noted that: 1) the term "removing" can be interpreted as "separating" such that any process whereby the solids of a culture medium are separated away from the culture medium would appear to be encompassed by this step; 2) step B) of claim 77 does not require removal of *all* solids from the medium, as long as any number of solids (e.g., cells) are removed or separated from the medium, the limitation of "removing solids including cells from the medium" would appear to be satisfied; and 3) this step is not limited to centrifugation and encompasses removing or transferring a portion of the culture medium, comprising both solids *and* liquid.

Regarding step C) of claim 77, the step of "purifying said L-amino acid from the medium obtained in step B)", it is noted that: 1) "the medium obtained in step B)" is not required to have *all* solids removed, thus, "the medium obtained in step B)" from which the L-amino acid is purified can be a mixture of solids and liquid, requiring only that at least some of the solids (e.g., cells) be removed or separated from the medium prior to "purifying said L-amino acid"; 2) it is well-known in the prior art that bacterially-produced L-amino acid is purified either as a secreted form or from the cell itself and thus, the L-amino acid that is purified in step C) is not limited to an L-amino acid that is secreted by the bacterium into the medium and can instead be intracellular, *i.e.,* inside the

bacterium; and 3) purification is a term of degree and there is no recited or required level of purification of the L-amino acid in the method step.

As noted in the prior Office action and undisputed by applicant, one would have reasonably considered removing a portion of the culture medium for optical density measurement to be encompassed by a step of "removing…cells from the medium" of step B), wherein the remaining culture medium is the "medium obtained in step B)." And, when the "amino acid" of step C) is intracellular, *i.e.,* inside the *E. coli* cell, then centrifugation after removing the portion of cells for optical density measurement and preparing a cell extract to remove cellular debris is considered to be purifying the intracellular L-amino acid from the "medium obtained in step B)", thus satisfying the limitations of step C). When the solids including cells of the remaining culture medium are considered to be a contaminant, then centrifugation after removing the portion of cells for optical density measurement is necessarily purifying L-amino acids from the solids including cells present in the "medium obtained in step B)", thus satisfying the limitations of step C).

Although the claims need not be so narrowly interpreted, the combination of references teaches at least 3 "distinct", "manipulative" steps – culturing, removing cells for optical density measurement, and centrifugation, optionally followed by preparing a cell lysate. As such, even though the claims do not require 3 "distinct", "manipulative" steps, the combination of references teaches such 3 "distinct", "manipulative" steps.

Applicant argues that Kobayashi, by teaching only manipulation of the post-centrifugation pellet, teaches away from purifying an L-amino acid. Applicant appears to

take the position that the term “purifying” must be interpreted as encompassing “ion exchange, concentration and crystalline fraction methods”, and that this “definition” must not be ignored. However, the specification does not appear to "define” the term “purifying” to be exclusively “ion exchange, concentration and crystalline fraction methods” and instead appears to provide these as merely exemplary methods of what is intended as being encompassed by “purifying”. In accordance with MPEP 2111.01.II, the claims have not been so narrowly interpreted. If applicant intends for the term “purifying” to be limited to “ion exchange, concentration and crystalline fraction methods”, applicant may amend the claims accordingly. As noted by MPEP 2111, "Applicant always has the opportunity to amend the claims during prosecution”.

While there is no dispute that the objective of the method of the combination of cited references would not be to produce an L-amino acid, the standard for establishing a *prima facie* case of obviousness does not appear to require that the prior art’s rationale be the same as applicant’s. According to MPEP 2144.IV, “The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant”.

Also, while applicant argues that the combination of references fails to acknowledge an increased amount of L-threonine, this again appears to be an improper standard for establishing a *prima facie* case of obviousness. Applicant acknowledges that the host cell of Kobayashi is that same as the “bacterium” as recited in claim 77,

part A). See particularly p. 6, middle of the instant remarks. According to MPEP 2112.02, "When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process". Also, MPEP 2112 acknowledges, "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103." Here, there is no evidence of record that the cell of Kobayashi does not produce a greater amount of L-amino acid and because the bacterium of Kobayashi is the same as that recited in claim 77, it would appear that the bacterium of Kobayashi also produces a greater amount of L-amino acid, including L-threonine.

Thus, at least for the reasons of record and those set forth above, the examiner maintains the position that the claimed invention would have been *prima facie* obvious at the time of the invention.

Claim Rejections – Double Patenting

[11] The provisional obviousness-type double patenting rejection of claims 77-84 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 6-7 of co-pending Application No. 11/106,455 is withdrawn in view of applicant's submission of a terminal disclaimer.

Conclusion

[12] Status of the claims:

Claims 77-84 are pending.

Claims 77-84 are rejected.

No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656